UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,982	05/02/2006	Makoto Koizumi	06189/HG	2978

1933 7590 02/19/2008

FRISHAUF, HOLTZ, GOODMAN & CHICK, PC
220 Fifth Avenue
16TH Floor
NEW YORK, NY 10001-7708

EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
02/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,982	KOIZUMI, MAKOTO	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/30/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-54* is/are pending in the application.

4a) Of the above claim(s) *8-11 and 44-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 12-43, and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05/02/2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :05/02/2006, 06/23/2006, & 08/03/2006.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of claims 1-5, 12-43, and 52-54 of Group I (oligonucleotides and kits comprising oligonucleotides) in the reply filed on 11/30/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-11 and 44-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 19, 2006.

Priority

2. It is noted that English translations of the foreign priority documents have not been provided.

Drawings

3. New corrected drawings of Figure 1 in compliance with 37 CFR 1.121(d) are required in this application because there are parenthetical remarks on this figure. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title should reflect that the claimed invention is to oligonucelotides having a 2'-O,4'-C-ethylene nucleotide in the third position of the 3' end. The reference to "method" in the current title should be deleted as this is not the elected invention.

5. The use of the trademark CHROMOLITH® has been noted in this application. It and any other trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is advised to scan the entire application to ensure trademark usage in all the places where it appears in the application is in compliance with the current office guidelines.

Sequence Rules Compliance

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the

requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Pages 64-79, 86, and 88-92 respectively contain sequences without SEQ ID NOs. If these sequences are included in the sequence listing provide by Applicant, the specification should be amended to include the SEQ ID NOs. If these sequences were not included in the sequence listing filed 05/02/2006. Applicant should provide a substitute sequence listing and a CRF that include those sequences.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-5, 12-43, and 52-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. In claims 1 and 2, the recitation of an " oligonucleotide comprising . . . (b) . . . having nucleotides complementary to the nucleotide sequence of the target gene . . . " is indefinite. First it is indefinite as to what is meant by "comprising . . . (b) . . having ". It appears that recitation of "having" is redundant as "comprising" is already recited. It may be intended that the oligonucleotide comprises an additional element which could be designated as "(c)". Second it is indefinite as to what is meant by "nucleotides complementary to the nucleotide sequence of the target gene". Does this mean the complementary nucleotides can be in any order in the oligonucleotide, or does it mean that a region of the oligonucleotide is complementary to the nucleotide sequence of the target gene, or is some other meaning intended. Third it is indefinite as to what is meant by "the nucleotide sequence of the target gene". By reciting "the", indication is given that the sequence is a singular and specific sequence. However the sequence is not defined. There is insufficient antecedent basis in the claims for the limitation of "the nucleotide sequence".

10. Claims 3 and 4 are indefinite. It is indefinite as to what is meant by "nucleotides complementary to the nucleotides of the target gene". Does this mean the complementary nucleotides and nucleotides of the target gene can be in any order, or does it mean that a region of the oligonucleotide is complementary to a region of the target gene, or is some other meaning intended.

11. As claims 1-4 are indefinite, dependent claims 20-43 are also indefinite.

12. Claims 12-17 are indefinite. It is indefinite as to what is meant by “nucleotides are complementary to the nucleotide sequence of a target gene”. First, does this mean the complementary nucleotides and nucleotides of the target gene can be in any, or does it mean that a region of the oligonucleotide is complementary to a region of the target gene, or is some other meaning intended. Second it is indefinite as to what is meant by “the nucleotide sequence of the target gene”. By reciting “the", indication is given that the sequence is a singular and specific sequence. However the sequence is not defined. There is insufficient antecedent basis in the claims for the limitation of “the nucleotide sequence”.

13. The term "a sequence of interest" in claims 12-17 is a relative term which renders the claim indefinite. The term "a sequence of interest" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "a sequence of interest" renders the oligonucleotide capable of amplifying” indefinite.

14. Claims 14 and 15 recites the limitation "the reference nucleotide of a target gene". There is insufficient antecedent basis for this limitation in the claim.

15. Claims 15-17 recite the limitation "the nucleotide of a reference gene". There is insufficient antecedent basis for this limitation in the claim.

16. Claims 16 and 17 recite the limitation "the mutant nucleotide of a target gene". There is insufficient antecedent basis for this limitation in the claim. Furthermore, the

preambles recite “gene polymorphism" which is not limited to "the", that is one singular mutant nucleotide.

17. As claims 12-17 are indefinite, dependent claims 52-54 are also indefinite.

18. The term "disease-associated gene" in claims 20, 23, 29, 25, and 41 is an undefined term which renders the claims indefinite. The term "causative gene" is not defined by the claims, the specification does not provide a limiting definition, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claims (MPEP § 2171 requirement (B)).

19. The term "drug metabolizing gene" in claims 26, 32, and 38 is an undefined term which renders the claims indefinite. The term "drug metabolizing gene" is not defined by the claims, the specification does not provide a limiting definition, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claims (MPEP § 2171 requirement (B)).

20. The term "causative gene" in claims 24, 30, 36, and 42 is an undefined term which renders the claims indefinite. The term "causative gene" is not defined by the claims, the specification does not provide a limiting definition, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claims (MPEP § 2171 requirement (B)).

21. The terms "a dopamine D3 receptor", “an angiotensin precursor”, “a blood coagulation factor VIII” in claims 25, 31, 37, and 43 are undefined terms which renders the claims indefinite. The terms "a dopamine D3 receptor", “an angiotensin precursor”, “a blood coagulation factor VIII” are not defined by the claims, the specification does not

provide a limiting definition, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claims (MPEP § 2171 requirement (B)).

Applicant is advised to carefully review the claims and to make the claim language consistent with U.S. practice.

Claim Rejections - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. Claims 1-5, 23, 29, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Latorra et al. (published online on 06/04/2003, cited on the IDS filed on 08/03/2006) and Koizumi et al. (2003, cited on the IDS filed on 08/03/2006).

Regarding claims 1, 2, 5, 23, and 29, Latorra et al. teach an oligonucleotide which is 21 bases (any one of the forward primers in Table 1) comprising:
(a) a 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (by teaching that the LNA nucleotide can be placed in any of the four positions, including the third position, from the 3' end of an oligonucleotide as given in Table 1); and

(b) a nucleotide complementary to the reference nucleotide of a target gene of pUC19 at the 3'-end position thereof (see Table 1) which can be the mutant nucleotide (see 2nd paragraph on p. 82), and

(c) nucleotides complementary to the nucleotide sequence of the target genes of pUC19 and the disease causing gene of cystic fibrosis which is the CTRF gene at the other positions (see p. 80, 3rd paragraph and see Table 1).

Regarding claims 3-5 and 41, Latorra et al. teach an oligonucleotide which is 21 bases (any one of the forward primers in Table 1) comprising:

(a) a nucleotide at the 3'-end of the oligonucleotide which is a nucleotide complementary to the reference/wild type nucleotide of a target gene and teach a nucleotide at the 3'-end of the oligonucleotide which is a nucleotide complementary to the mutant nucleotide of a target gene (see Table 1 and see p. 80, 3rd paragraph),

(b) wherein a nucleotide which is the second nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and wherein the second nucleotide of each oligonucleotide of claims 3 and 4 is a nucleotide that is not complementary respectively to the nucleotide of a reference/wild type gene and the mutant gene (see p. 80, 3rd paragraph, Table 1, and Figure 3).

(c) nucleotides complementary to the nucleotides of the target gene at other positions; and

(d) a nucleotide which is the third nucleotide from the 3'-end of each oligonucelotide is a 2'-O,4'-C-methylene nucleotide (LNA) unit (see Table1).

Regarding claims 1-5, Latorra et al. do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit.

Regarding claims 1-5, Koizumi et al. teach both 2'-O,4'-C-methylene nucleotide (LNA) units and 2'-O,4'-C-ethylene nucleotides (ENA) units (entire article, especially the Abstract). Koizumi et al. further teach in comparison studies that substitution of ENA units for LNA units leads to improved properties of oligonucleotides, including: *{i}* triplex formation having c3'-endo conformation at physiological pH (see Title and Conclusiont on p. 3272) and *{ii}* " ENA . . . [being] more nuclease-resistant than natural DNA and 2',4'-BNA/LNA" (see last sentence of 3rd paragraph of the body of the text on p. 3267 and Conclusion on p. 3272).

Regarding claims 1-5, Koizumi et al. do not specifically teach an oligonucelotide somprising an ENA units at the third position from the 3' end.

Latorra et al. teach oligonucelotides comprising LNA units at the third position from the 3' of an oligonucleotide. Latorra et al. do not specifically teach ENA units. Koizumi et al. teach that oligonucelotides can comprise either LNA units or ENA units. Furthermore Koizumi et al. teach that substitution of ENA units for LNA units in a oligonucleotide results in improved properties of that nucleotide. Because both Latorra et al. and Koizumi et al. teach oligonucleotides comprising LNA units, it would have been obvious to one skilled in the art to substitute an ENA unit as taught by Koizumi et al. for the LNA unit as taught by Latorra et al. in order to achieve the predictable result of an oligonucleootide comprising an ENA unit at the third position from the 3' end.

24. Claims 12-19 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Latorra et al. (published online on 06/04/2003, cited on the IDS filed on 08/03/2006), Koizumi et al. (2003, cited on the IDS filed on 08/03/2006), and Weston et al. (U.S. Patent No. 6,391,593 issued 2002).

Regarding claims 12, 13, 19, and 52 Latorra et al. teach an oligonucleotide which is 21 bases (any one of the forward primers in Table 1) comprising:
(a) a first oligonucleotide which is a forward primer wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (by teaching that the LNA nucleotide can be placed in any of the four positions, including the third position, from the 3' end of an oligonucleotide as given in Table 1) wherein the forward primer can be one which is either complementary to the reference/wild type gene or the mutant gene (see p. 80, 3rd paragraph and see Table 1) and where the gene polymorphism is a single nucleotide polymorphism (see 1st sentence on p. 79) in the disease causing gene of cystic fibrosis which is the CTRF gene at the other positions (see p. 80, 3rd paragraph and see

Table 1); and

(b) a second oligonucleotide which is a reverse primer (see Table 1),

(c) the Taq DNA polymerase (see 2nd paragraph on p. 81), and

(d) a PCR buffer (see 2nd paragraph on p. 81).

Regarding claims 14, 18, 19, and 53, Latorra et al. teach an oligonucleotide which is 21 bases (any one of the forward primers in Table 1) comprising:
(a) a first oligonucleotide which is forward primer 1 wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (by teaching that the LNA nucleotide can be placed in any of the four positions, including the third position, from the 3' end of an oligonucleotide as given in Table 1) wherein the forward primer can be one which is either complementary to the reference/wild type gene or the mutant gene (see p. 80, 3rd paragraph and see Table 1) and where the gene polymorphism is a single nucleotide polymorphism (see 1st sentence on p. 79) in the disease causing gene of cystic fibrosis which is the CTRF gene at the other positions (see p. 80, 3rd paragraph and see Table 1).;

and

(b) a second oligonucleotide which is forward primer 2 wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide,

and the other nucleotides are natural nucleotides (by teaching that the LNA nucleotide can be placed in any of the four positions, including the third position, from the 3' end of an oligonucleotide as given in Table 1);

(c) a third oligonucleotide which is reverse primer 1 capable of amplifying a sequence of interest together with the forward primer 1 (see Table 1)

(d) the Taq DNA polymerase (see 2nd paragraph on p. 81), and

(e) a PCR buffer (see 2nd paragraph on p. 81).

Regarding claims 15, 16, 18, 19, and 54, Latorra et al. teach an oligonucleotide which is 21 bases (any one of the forward primers in Table 1) comprising:

(a) a first oligonucleotide which is a forward primer having

(i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see p. 80, 3rd paragraph and see Table 1) and where the gene polymorphism is a single nucleotide polymorphism (see 1st sentence on p. 79) in the disease causing gene of cystic fibrosis which is the CTRF gene at the other positions (see p. 80, 3rd paragraph and see Table 1);

(ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see p. 80, 3rd paragraph and see Table 1);

(iii) the other nuceltodies are complentary respectively to the nucleotides of the target gene and mutant gene (see p. 80, 3rd paragraph and see Table 1); and

(iv) a 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is

defined as the first nucleotide, and the other nucleotides are natural nucleotides (by teaching that the LNA nucleotide can be placed in any of the four positions, including the third position, from the 3' end of an oligonucleotide as given in Table 1) ;

(b) a second oligonucleotide which is one of the reverse primers capable of amplifying a sequence of interest together with the forward primers (see Table 1)

(c) the Taq DNA polymerase (see 2nd paragraph on p. 81), and

(d) a PCR buffer (see 2nd paragraph on p. 81).

Regarding claims 17-19 and 54, Latorra et al. teach an oligonucleotide which is 21 bases (any one of the forward primers in Table 1) comprising:

(a) a first oligonucleotide which is a forward primer having

(i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see p. 80, 3rd paragraph and see Table 1) and where the gene polymorphism is a single nucleotide polymorphism (see 1st sentence on p. 79) in the disease causing gene of cystic fibrosis which is the CTRF gene at the other positions (see p. 80, 3rd paragraph and see Table 1);

(ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see p. 80, 3rd paragraph and see Table 1);

(iii) the other nuceltodies are complentary respectively to the nucleotides of the target gene and mutant gene (see p. 80, 3rd paragraph and see Table 1); and

(iv) a 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (by

teaching that the LNA nucleotide can be placed in any of the four positions, including the third position, from the 3' end of an oligonucleotide as given in Table 1) ;

(b) a second oligonucleotide having a

(i) a 3' end nucleotide complementary to either the reference/wild type nucleotide or the mutant nucleotide (see the alternate forward primers 1-3 and the reverse primers 1-3 in Table 1 and see p. 80, 3rd paragraph);

(ii) a second nucleotide which is not complementary to either the reference/wild type nucleotide or the mutant nucleotide (see the alternate forward primers 1-3 and the reverse primers 1-3 in Table 1 and see p. 80, 3rd paragraph);

(iii) the other nuceltodies are complentary respectively to the nucleotides of the target gene and mutant gene (see p. 80, 3rd paragraph and see Table 1); and

(ii) forward primer 3 wherein 2'-O,4'-C-methylene nucleotide (LNA) unit (see Figure 1) is the third nucleotide from the 3'-end of the oligonucleotide, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides (by teaching that the LNA nucleotide can be placed in any of the four positions, including the third position, from the 3' end of an oligonucleotide as given in Table 1);

(c) a third oligonucleotide which is any one of the respective reverse primers capable of amplifying a sequence of interest together with the forward primer (see Table 1)

(d) the Taq DNA polymerase (see 2nd paragraph on p. 81), and

(e) a PCR buffer (see 2nd paragraph on p. 81).

Regarding claims 12-18, Latorra et al. do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit and do not specifically teach a kit.

Regarding claims 12-18, Koizumi et al. teach both 2'-O,4'-C-methylene nucleotide (LNA) units and 2'-O,4'-C-ethylene nucleotides (ENA) units (entire article, especially the Abstract). Koizumi et al. further teach in comparison studies that substitution of ENA units for LNA units leads to improved properties of oligonucleotides, including: *{i}* triplex formation having c3'-endo conformation at physiological pH (see Title and Conclusiont on p. 3272) and *{ii}* " ENA . . . [being] more nuclease-resistant than natural DNA and 2',4'-BNA/LNA" (see last sentence of 3rd paragraph of the body of the text on p. 3267 and Conclusion on p. 3272).

Regarding claims 12-18, Koizumi et al. do not specifically teach a kit.

Regarding claims 12-18, Weston et al. teach kits comprising olignucleotides with LNA units, DNA polymerases, and PCR buffers (see column 7 lines 41-51 and see claims 20 and 21).

Latorra et al. teach oligonucelotides comprising LNA units at the third position from the 3' of an oligonucleotide. Latorra et al. do not specifically teach ENA units. Koizumi et al. teach that oligonucelotides can comprise either LNA units or ENA units. Furthermore Koizumi et al. teach that substitution of ENA units for LNA units in a oligonucleotide results in improved properties of that nucleotide. Because both Latorra

et al. and Koizumi et al. teach oligonucleotides comprising LNA units, it would have been obvious to one skilled in the art to substitute an ENA unit as taught by Koizumi et al. for the LNA unit as taught by Latorra et al. in order to achieve the predictable result of an oligonucleootide comprising an ENA unit at the third position from the 3' end.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the oligonucleotides of Latorra et al. and Koizumi et al. by incorporating them in a kit as suggested by Weston et al. with a reasonable expectation of success. The motivation to do so is provided by Weston et al. who teach the convenience and advantage of kits comprising oligonucleotides, DNA polymerase, and PCR buffers (see column 7 lines 41-51). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

25. Claims 20-22, 24-28, 30-40, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Latorra et al. and Koizumi et al. as applied to claims 1-4 above, and further in view of Stanton et al. (US publication No. 20010034023 published 2001).

Latorra et al. and Koizumi et al. teach as noted above.

Latorra et al. and Koizumi et al. do not teach the limitations of claims 20-22, 24-28, 30-40, and 42-43.

Regarding claims 20-22, 24-28, 30-40, and 42-43 Stanton et al. teach oligonucleotides/primers for detecting drug metabolizing genes (entire publication, especially paragraph 0143) which are glutathione transferase, N-acetyltransferase (see paragraph 0262), Human cytochrome P4502C9 (see Table 2121 at paragraph 1058))

which are associated with Alzheimer's disease (see paragraph 0023) and teach the target gene which is HLA (see paragraph 0760).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the oligonucleotides of Latorra et al. and Koizumi et al by making oligonucleotides to detect drug metabolizing genes as suggested by Stanton et al. with a reasonable expectation of success. The motivation to do so is provided by Stanton et al. who teach that such oligonucleotides can be used in methods: " . . . for identifying and utilizing variances in genes relating to efficacy and safety of medical therapy and other aspects of medical therapy" (see Abstract). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

26. No claim is free of the prior art.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Examiner, Art Unit 1637
February 14, 2008